EXAMINER'S AMENDMENT

Applicant's amendment filed on 09-09-2008 has been entered. Claims 1, 8, 10-15, 19, 20, 23-27, and 29-30 are currently pending. Applicant's representative was contacted on September 25, 2008 to amend the following claims before allowance: claim 1, to properly recite the preamble to the Markush group, claims 10, 12, 24 and 26, to correct the recitation of "and/or", claims 1 and 20, to delete the recitation "for tumor imaging" in the preamble of the claims, and claims 10, 14 and 24 to clearly define what is coupled to what.

Authorization for the examiner's amendment was given in a telephone interview with Kelly K. Reynolds, on September 26, 2008.

With respect to the proposed claims, an examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it must be submitted no later than the payment of the issue fee.

In the abstract,

The abstract has been rewritten as follows:

Described is a diagnostic conjugate comprising (a) a transmembrane module (TPU), (b) an address module (AS), preferably an antisense peptide nucleic acid (PNA), and (c) a signalling module (SM). The conjugate is useful for intracellular imaging, preferably via MRI, and e.g., for differentiation between tumor-and non-tumor cells.

In the claims,

The claims have been rewritten as follows:

1. A diagnostic conjugate having the structure: transmembrane module (TPU) coupled via a spacer to an address module (AS) coupled via a spacer to a signalling module (SM); wherein

- the transmembrane module is a cell-penetrating human transmembrane peptide comprising the amino acid sequence KMTRQTWWHRIKHKC (SEQ ID NO: 2), MTRQTFWHRIKHKC (SEQ ID NO: 3) or KHKIRHWFTQRTMC (SEQ ID NO: 4),

- the address module is a peptide nucleic acid (PNA) antisense to and hybridizing with a mRNA selected from the group consisting of c-myc-, c-ras-, hern-, sstl, or sst2-mRNA, and

- the signalling module is a compound trapping Gadolinium.

10. The diagnostic conjugate of claim 1, wherein the transmembrane module (TPU) is coupled to the address module (AS) via a covalently cleavable spacer I or the address module (AS) is coupled to the signalling module (SM) via a covalently non-cleavable spacer II.

12. The diagnostic conjugate of claim 10, wherein spacer I or spacer II comprises polylysine or polyglycine.

13. The diagnostic conjugate of claim 12, wherein spacer II carries a FITC-label.

14. The diagnostic conjugate of claim 1 having the following structure: transmembrane module (TPU) - spacer I comprising a cleavable disulfide bridge - address module (AS) - spacer II - signalling module (SM).

20. A diagnostic conjugate having the structure: transmembrane module (TPU) coupled via a cleavable spacer I to an address module (AS) coupled via a spacer II to a signalling module (SM); wherein

- the transmembrane module (TPU) is a cell-penetrating human transmembrane peptide comprising the amino acid sequence KMTRQTWWHRIKHKC (SEQ ID NO: 2), MTRQTFWHRIKHKC (SEQ ID NO: 3) or KHKIRHWFTQRTMC (SEQ ID NO: 4),

- the address module (AS) is a peptide nucleic acid (PNA) antisense to and hybridizing with a mRNA selected from the group consisting of c-myc-, c-ras-, hern-, sstl, or sst2-mRNA, and

- the signalling module (SM) is diethylenetriaminetriaminepentaaceticacid acid (DTPA).

24. The diagnostic conjugate of claim 20, wherein the address module (AS) is coupled via a covalently cleavable spacer I to the transmembrane module (TPU) or the address module (AS) is coupled to the diethylenetriaminetriaminepentaaceticacid acid (DTPA) via a covalently non-cleavable spacer II.

26. The diagnostic conjugate of claim 20, wherein spacer I or spacer II comprises polylysine or polyglycine.

Reasons for allowance

The following is an examiner's statement of reasons for allowance: The prior art of record does not teach or suggest a diagnostic conjugate for tumor imaging having the structure:

transmembrane module (TPU) coupled via a spacer to an address module (AS) coupled via a spacer to a signalling module (SM); wherein

- the transmembrane module is a cell-penetrating human transmembrane peptide comprising the amino acid sequence KMTRQTWWHRIKHKC (SEQ ID NO: 2), TRQTFWHRIKHKC (SEQ ID NO: 3) or KHKIRHWFTQRTMC (SEQ ID NO: 4) transport peptide capable of penetrating the plasma membrane,

- the address module is a peptide nucleic acid (PNA) antisense to and hybridizing with a mRNA selected from the group consisting of c-myc-, c-ras-, hern-, sstl, or sst2-mRNA, and

- the signalling module is a compound trapping Gadolinium.

The closest prior art of Braun et al. and Caravan et al. does not provide disclosure for the inclusion of a human transmembrane peptide, in particular one having SEQ ID NO: 2, 3 or 4. In addition, the instant invention differs from the closest prior art of Braun et al. and Caravan by providing a conjugate which allows for rapid accumulation of the gadolinium contrast agent in the cells and allows distinction between non-tumor and tumor cells due to the specific retention in tumor-cells. Such was not possible with the Gd-agents of the prior art. It was not suggested in

the prior art to use peptide nucleic acids for MRI. Example 2 of the present invention, however, demonstrates that such use is possible with the claimed conjugates.

Withdrawn rejections in response to Applicant arguments or amendments

Claim Rejections - 35 USC § 112- First paragraph- Scope of Enablement

The previous rejection of claims 1, 8, 10-15, 19, 20, 23-27, and 29-30 as failing to comply with the enablement requirement, has been withdrawn in view of Applicants' amendment to claims 1, 10, 20 and 24-27, and further in view of Applicants remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art, at the time of filing the present application.

The instant claims are drawn a diagnostic conjugate for tumor imaging having the structure: transmembrane module (TPU) coupled via a spacer to an address module (AS) coupled via a spacer to a signalling module (SM); wherein

- the transmembrane module is a cell-penetrating human transmembrane peptide comprising the amino acid sequence KMTRQTWWHRIKHKC (SEQ ID NO: 2), TRQTFWHRIKHKC (SEQ ID NO: 3) or KHKIRHWFTQRTMC (SEQ ID NO: 4) transport peptide capable of penetrating the plasma membrane,

- the address module is a peptide nucleic acid (PNA) antisense to and hybridizing with a mRNA selected from the group consisting of c-myc-, c-ras-, hern-, sstl, or sst2-mRNA, and

- the signalling module is a compound trapping Gadolinium.

The disclosure provides sufficient guidance for the transmembrane module (TPU) coupled to the address module (AS) via a cleavable spacer or non-cleavable spacer so as permit the peptide nucleic acid to hybridize with the c-myc, c-ras-, hern-, sstl or sst2-mRNA target. In addition,

Applicants have demonstrated that in the present application $Gd(DTPA)(H20)^{2-}$ can enter the target cell with the rest of the conjugate. Therefore, other compounds trapping Gd and having a similar low hydrophobicity as Gd(DTPA)(H20)2- or even a higher hydrophobicity will likewise enter the target cell, since compounds having higher hydrophobicity pass through the cell membrane much more easily than does $Gd(DTPA)(H20)^{2-}$. To avoid undesired interactions between the trapping Gd and the rest of the conjugate, a spacer is used to eliminate steric hindrances. Thus, Applicants have provided sufficient disclosure to show that Gd-trapping signalling modules enter the target cell together with the rest of the conjugate.

Claim Rejections - 35 USC § 103

The previous rejection of claims 1, 15, 20, 30, and 31 under 35 USC § 103 as being unpatentable over Braun et al., (US patent No. 6,821,948), in view Cavaran et al., (*Bioconjug Chem.* 1999 pp. 361-70) has been withdrawn in view of Applicants' amendment to claims 1, 10, 20 and 24-27, and further in of Applicants' remarks.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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